Subcutaneous CT-P13 monotherapy vs combination with immunomodulation when switching from intravenous infliximab in inflammatory bowel disease – A Multicentre, Randomised Withdrawal Trial

Short Title - **M**onotherapy with **IN**flix**IM**ab when sw**I**tching to **S**ubcutaneous th**E**rapy
Acronym - **MINIMISE**

Trial Protocol

Version 1.0 (07JUN22)

Trial Identifiers

EudraCT Number: 2021-006803-13
IRAS Number: 1005499
REC Number: 22/EE/0166
ISRCTN Number: 95420128

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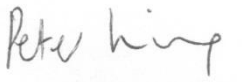
SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature: 

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1 Study Synopsis and General Information

Title of clinical trial	Subcutaneous CT-P13 monotherapy vs combination with immunomodulation when switching from intravenous infliximab in inflammatory bowel disease – A Multicentre, Randomised Withdrawal Trial
Protocol Short Title	**M**onotherapy with **IN**flix**IM**ab when sw**I**tching to **S**ubcutaneous th**E**rapy
Protocol Acronym	MINIMISE
Sponsor name	Guy's and St Thomas' NHS Foundation Trust
Chief Investigator	Dr Peter Irving
EudraCT number	2021-006803-13
Trial Phase	IV
Medical condition or disease under investigation	Inflammatory Bowel Disease
Purpose of clinical trial	To investigate the need for continuing combination therapy when switching patients on combined IV infliximab and immunomodulation to subcutaneous (SC) CT-P13
Objectives	**Primary objective** • To determine whether discontinuing immunomodulation after switching from IV infliximab to SC CT-P13 is non-inferior to continuing combination therapy with a thiopurine in terms of occurrence of free antibody positivity at week 24 **Secondary objectives** • To assess if discontinuing immunomodulators after switching from IV infliximab to SC CT-P13 results in lower infliximab levels at weeks 8, 16 and 24 • To assess if discontinuing immunomodulators after switching from IV infliximab to SC CT-P13 results in increased anti-drug antibodies at weeks 8, 16 and 24; and by Week 24 • To assess the efficacy and tolerability of therapy in participants continuing and discontinuing immunomodulators after switching from IV infliximab to SC CT-P13 • To assess acceptability of switching from IV to SC treatment at Week 24/ Early termination, regardless of randomisation allocation

	• To assess quality of life in patients switching from IV to SC treatment at Week 24/ Early termination, regardless of randomisation allocation • To understand how baseline TGN levels and DQA1*05 positivity affect infliximab drug levels and anti-drug antibody production, regardless of randomisation allocation.
Endpoints	**Primary Endpoint** • Free antibody positivity (i.e. ≥10 ng/mL) at week 24 in patients continuing and discontinuing thiopurines after switching from IV infliximab to SC CT-P13 **Secondary Endpoints** • Infliximab drug levels at weeks 8, 16 and 24 in participants continuing and discontinuing immunomodulators after switching from IV infliximab to SC CT-P13 • Total anti-drug antibodies at weeks 8, 16 and 24 and free anti-drug antibodies at weeks 8 and 16 in participants continuing or discontinuing immunomodulators after switching from IV infliximab to SC CT-P13 • Anti-drug antibody positivity (free and total) by week 24 in participants continuing or discontinuing immunomodulators after switching from IV infliximab to SC CT-P13 • Efficacy of therapy by week 24/ Early termination measured as the proportion of participants developing clinically active disease (HBI> 4 or SCCAI>2), biochemically active disease (CRP >5 mg/l and/or faecal calprotectin >250mcg/g), and both clinically and biochemically active disease, in participants continuing or discontinuing immunomodulators after switching from IV infliximab to SC CT-P13 • Tolerability of treatment through to week 24/ Early termination measured as rate of AE and SAEs in participants continuing or discontinuing immunomodulators after switching from IV infliximab to SC CT-P13 • Quality of life in participants switching from IV to SC treatment at Week 24/ Early Termination, regardless of randomisation allocation, measured using the IBD-Control Questionnaire.

	• Proportion of participants having to revert back to IV in each randomisation arm • Acceptability of switching from IV to SC treatment measured using a treatment acceptability questionnaire at week 24/ Early termination • Infliximab drug levels and anti-drug antibodies positivity at weeks 8, 16, and 24 in participants with positive and negative HLA DQA1*05, regardless of randomisation allocation • Infliximab drug levels and anti-drug antibodies positivity at weeks 8, 16, and 24 in participants with baseline TGN concentrations greater/ equal to vs less than 125 pmol/8x10^8 RBC and greater/ equal to vs less than 235 pmol/8x10^8 RBC, regardless of randomisation allocation. **Exploratory Endpoints** • Immunophenotyping using flow-cytometry on whole blood samples at screening and week 24/ Early termination[9]
Trial Design	Phase IV, Open label, Randomised controlled withdrawal design
Sample Size	102 participants
Summary of eligibility criteria	**Inclusion criteria:** • Aged 18 years or over • Diagnosis of Crohn's disease, ulcerative colitis or IBD-U for at least 6 months at the time of commencement of SC CT-P13 • A clinical decision has been made to switch from intravenous infliximab to SC CT-P13 • On stable IV infliximab at 5mg/kg Q8W for at least 22 weeks at the time of commencement of SC CT-P13 • On azathioprine or mercaptopurine for at least 3 months, at a stable dose for at least 4 weeks at the time of commencement of SC CT-P13 • Clinical remission defined by HBI ≤4 or SCCAI ≤2 at screening • Infliximab levels above or equal to the lower therapeutic level (as per local lab) at the time of the final or penultimate IFX infusion • Written informed consent to participate • Sufficient English to understand the study and sign informed consent, or available local interpreting service

	Exclusion criteria: • Not willing or able to switch to subcutaneous (SC) treatment • Evidence of clinically active severe infections such as, bacterial sepsis, active viral infection and opportunistic infections. Severity as judged by the investigator • Any clinically significant test results that in the opinion of the investigator should exclude the participant • In the opinion of the investigator, patient in whom withdrawal of the thiopurine would not be appropriate • Known allergy/ hypersensitivity/ intolerance to the active substance or excipients, or patients taking any medications which are contraindicated as per the IMPs SmPCs • Participation in an investigational trial that involves ongoing treatment with an investigational medicinal product at baseline • Pregnant women and women of child bearing potential who are planning to get pregnant during the trial
IMP dosage and route of administration	IMP: Participants randomised to continue their immunomodulator will do so at the same dose and frequency until the end of week 24, unless dose change is deemed necessary by the investigator. NIMP: SC CT-P13 will be administered every 2 weeks at a dose of 120mg SC, starting approximately 8 weeks after discontinuing IV infliximab (i.e. at the time of the baseline visit).
Prior treatment experience	On stable IV infliximab at 5mg/kg Q8W for at least 22 weeks at the time of commencement of SC CT-P13 On azathioprine or mercaptopurine for at least 3 months, at a stable dose for at least 4 weeks at the time of commencement of SC CT-P13
Maximum trial duration per patient	25 weeks
Version and date of protocol amendments	

2 Abbreviations and Glossary

AE	Adverse event
AR	Adverse reaction
ALT	Alanine Transaminase
BNF	British National Formulary
CD	Crohn's Disease
CI	Chief Investigator
CRP	C-Reactive Protein
eCRF	Electronic Case Report Form
FBC	Full Blood Count
FCP	Faecal Calprotectin
GCP	Good Clinical Practice
GSTT	Guy's and St Thomas' NHS Foundation Trust
GP	General Practitioner
HBI	Harvey Bradshaw index
HRA	Health Research Authority
IBD	Inflammatory Bowel Disease
IBD-Q	Inflammatory Bowel Disease Questionnaire
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IFX	Infliximab
IME	Important medical event
IMDC	Independent Data Monitoring Committee
IMP	Investigational medicinal product
KHP-CTO	King's Healthcare Partners Clinical Trials Office
MHRA	Medicines and Healthcare Research Authority
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
PIS	Participant Information Sheet
Q8W	Every 8 weeks
REC	Research Ethics Committee
RN	Research Nurse
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SC	Subcutaneous
SSCAI	Simple Clinical Colitis Activity index
SOP	Standard Operating Procedure

SUSAR	Suspected Unexpected Serious Adverse Reaction
TGN	Thioguanine nucleotides
TMF	Trial Master File
TSC	Trial Steering Committee
UC	Ulcerative colitis
WOCP	Women of childbearing potential

3 Background and Rationale

3.1 Background

The current requirement for novel therapies in Inflammatory Bowel Disease

With an annual cost to the NHS of over £900 million, a rising incidence and a prevalence approaching 0.5%, inflammatory bowel disease (IBD) is a prominent and costly cause of chronic morbidity in the UK.
IBD comprises two conditions characterised by chronic, idiopathic inflammation of the intestine: ulcerative colitis (UC) and Crohn's disease (CD), both of which result in considerable morbidity, reduced quality of life and significant occupational loss. Goals of therapy include resolution of symptoms and induction of mucosal healing. Many patients have a sub-optimal or a non-sustained response to current therapies used to induce or maintain remission, or develop side effects from medications. All of these factors indicate a pressing need for novel therapeutic modalities.

Current treatment

Infliximab (IFX) is a well-established pharmacological treatment for the management of IBD, having been used in the last two decades as an effective and well tolerated treatment for both CD and UC. Whilst IFX is generally well tolerated, its major disadvantage relates to its immunogenicity which affects the majority of patients over time. In a recent large cohort from the UK, 64.5% of IFX-treated patients developed anti-IFX antibodies by week 52. When looking at neutralising antibodies (defined as antibodies detectable in the absence of drug), 31.8% of patients developed antibodies over 1 year[1].

Intravenous (IV) IFX is best used in combination with an immunomodulator, usually a thiopurine, as using an immunomodulator was associated with a hazard ratio of 0.39 for antibody development. Unfortunately, immunomodulation has disadvantages. For instance thiopurines are implicated in the development of lymphoma, non-melanoma skin cancers and urothelial tract cancers[2]. They are also poorly tolerated by many patients. This, combined with the development of less immunogenic monoclonal antibodies has led to a decreased use of IFX, simply in an attempt to avoid the use of immunomodulators.

Until recently the only available route of administration of IFX has been intravenous however a subcutaneous (SC) version of CT-P13 is now available. This carries clear advantages for patients in terms of convenience and is supported by recent trial data which have shown non-inferiority when compared to IV IFX after induction to week 30 (UEGW 2019)[3]. In addition, data from the same trial regarding patients switching from IV to SC CT-P13 show ongoing remission after switching[3].

3.2 Rationale

Recent research suggests that SC CT-P13 appears to be less immunogenic than IV CT-P13. In a clinical trial in IBD, by week 30 29.2% of IV patients had neutralising antibodies compared with only 3.0% of SC-treated patients. 13.6% of SC-treated patients had developed neutralising antibodies at any point during the 30 week follow up compared with 36.9% of IV-treated patients[3]. In view of these findings, there is a strong rationale for using SC CT-P13 as a monotherapy (without immunomodulators) which represents a further advantage over IV therapy and, in addition, brings it into line with other biologics that do not require combination therapy (vedolizumab, ustekinumab, golimumab and, to a lesser extent, adalimumab).

The current standard of care in the UK is that patients with IBD who have been receiving IV infliximab therapy are offered the option of switching to SC treatment. The transition to using SC has been expedited in many hospitals since the advent of the Covid-19 pandemic, as this allowed to reduce the number of patients needing to attend the hospital for infusions; and therefore reduce their risk of contracting COVID-19[4].

We propose to perform a randomised controlled trial of patients continuing or discontinuing immunomodulators when switching from combination IV therapy (IV IFX + immunomodulator), to SC CT-P13. We will stratify the treatment allocation by HLA-DQA1*05, as the presence of this genetic variant has been associated with an increased risk of immunogenicity, as approximately 90% of patients with this variant who were taking IFX monotherapy developing antibodies by 1 year[5].

4 Trial Objectives and Design

4.1 Trial Objectives

4.1.1 Primary Objective:

- To determine whether discontinuing immunomodulation after switching from IV infliximab to SC CT-P13 is non-inferior to continuing combination therapy with a thiopurine in terms of occurrence of free antibody positivity at week 24

4.1.2 Secondary Objectives:

- To assess if discontinuing immunomodulators after switching from IV infliximab to SC CT-P13 results in lower infliximab levels at weeks 8, 16 and 24
- To assess if discontinuing immunomodulators after switching from IV infliximab to SC CT-P13 results in increased anti-drug antibodies at weeks 8, 16 and 24; and by Week 24
- To assess the efficacy and tolerability of therapy in participants continuing and discontinuing immunomodulators after switching from IV infliximab to SC CT-P13
- To assess acceptability of switching from IV to SC treatment at Week 24/ Early termination, regardless of randomisation allocation
- To assess quality of life in patients switching from IV to SC treatment at Week 24/ Early termination, regardless of randomisation allocation
- To understand how baseline TGN levels and DQA1*05 positivity affect infliximab drug levels and anti-drug antibody production, regardless of randomisation allocation.

4.2 Trial Endpoints

4.2.1 Primary Endpoint:

- Free antibody positivity (i.e. ≥10 ng/mL) at week 24 in patients continuing and discontinuing thiopurines after switching from IV infliximab to SC CT-P13

4.2.2 Secondary Endpoints:

- Infliximab drug levels at weeks 8, 16 and 24 in participants continuing and discontinuing immunomodulators after switching from IV infliximab to SC CT-P13
- Total anti-drug antibodies at weeks 8, 16 and 24 and free anti-drug antibodies at weeks 8 and 16 in participants continuing or discontinuing immunomodulators after switching from IV infliximab to SC CT-P13

- Anti-drug antibody positivity (free and total) by week 24 in participants continuing or discontinuing immunomodulators after switching from IV infliximab to SC CT-P13
- Efficacy of therapy by week 24/ Early termination measured as the proportion of participants developing clinically active disease (HBI> 4 or SCCAI>2), biochemically active disease (CRP >5 mg/l and/or faecal calprotectin >250mcg/g), and both clinically and biochemically active disease, in participants continuing or discontinuing immunomodulators after switching from IV infliximab to SC CT-P13
- Tolerability of treatment through to week 24/ Early termination measured as rate of AE and SAEs in participants continuing or discontinuing immunomodulators after switching from IV infliximab to SC CT-P13
- Quality of life in participants switching from IV to SC treatment at Week 24/ Early Termination, regardless of randomisation allocation, measured using the IBD-Control Questionnaire. Each response to the 13 individual items scored as zero points for least favourable reply, one point for intermediate or indeterminate reply and two points for most favourable reply. The IBD-Control-8 subscore is calculated by summing scores for Q1a, Q1b, Q3a, Q3b, Q3c, Q3d, Q3e and Q3f resulting in a range of 0–16 (0=worst control). The IBD-Control-VAS scores are in the range 0–100 (0=worst control)
- Proportion of participants having to revert back to IV in each randomisation arm
- Acceptability of switching from IV to SC treatment measured using a treatment acceptability questionnaire at week 24/ Early termination
- Infliximab drug levels and anti-drug antibodies positivity at weeks 8, 16, and 24 in participants with positive and negative HLA DQA1*05, regardless of randomisation allocation
- Infliximab drug levels and anti-drug antibodies positivity at weeks 8, 16, and 24 in participants with baseline TGN concentrations greater/ equal to vs less than 125 pmol/8x10^8 RBC and greater/ equal to vs less than 235 pmol/8x10^8 RBC, regardless of randomisation allocation.

4.2.3 Exploratory Endpoints:

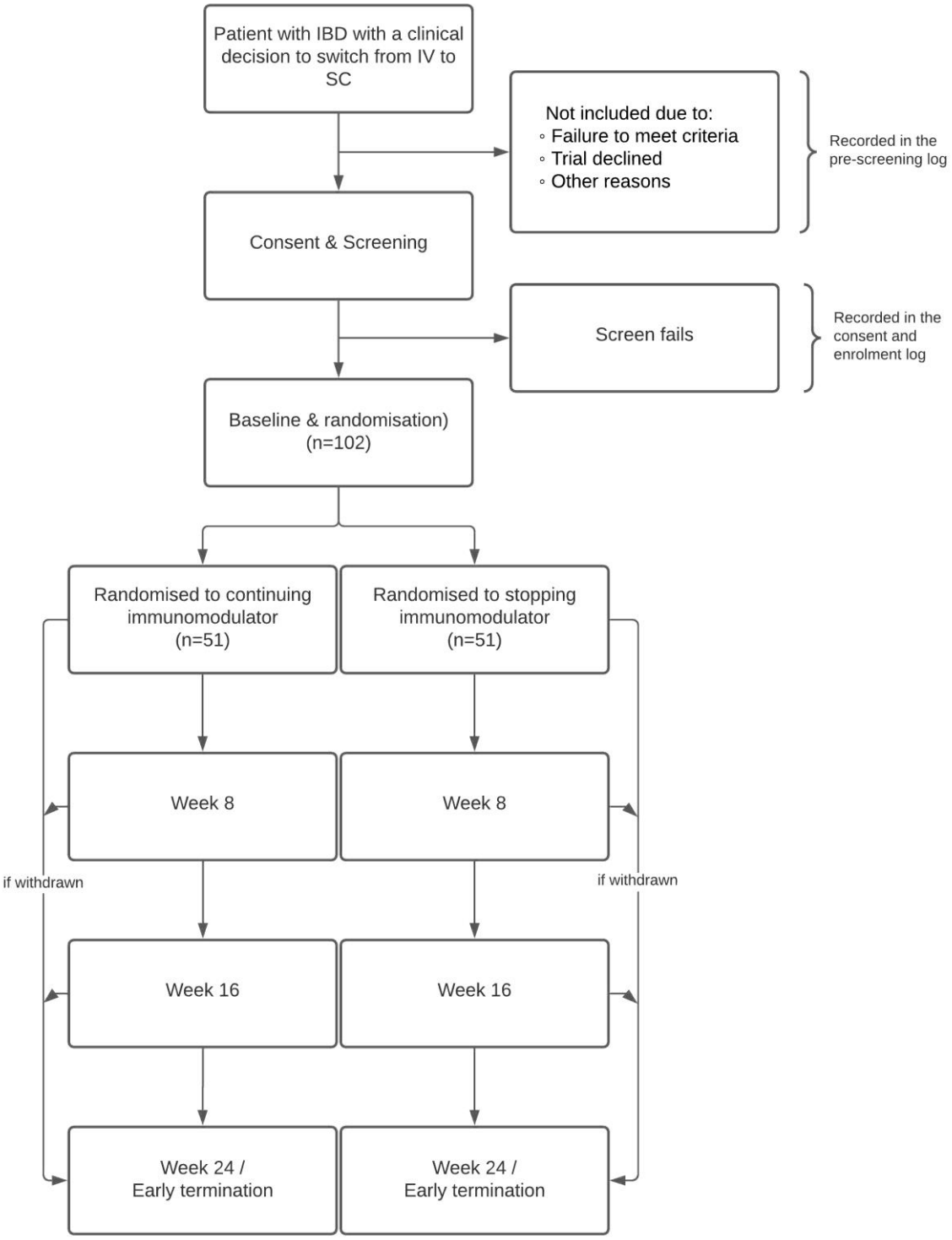
Immunophenotyping using flow-cytometry on whole blood samples at screening and week 24/ Early termination[9]

4.3 Trial Design

4.3.1 Overview

The MINIMISE trial is an open label, randomised controlled withdrawal trial investigating the need for continuing combination therapy with a thiopurine when switching patients from combined therapy (IV infliximab and immunomodulation) to subcutaneous (SC) CT-P13.

4.3.2 Trial flowchart



4.4 Schedule of events

	Screening (-9 weeks to -2 weeks)	Baseline (week 0)	Week 8 (±1 week)	Week 16 (±1 week)	Week 24 (±1 week)/ Early termination*
Written informed consent	X				
Eligibility assessment	X	X			
Pregnancy test for WOCBP	X	X			
Demographics	X				
Height and weight	X[B]				X[B]
Vital signs[A]	X	X	X	X	X
Dr review ± physical examination	X[C]	X[C]	X[CF]	X[CF]	X[C]
Medical and smoking history	X				
Randomisation		X			
IMP compliance check			X	X	X
First administration of SC CT-P13 and training		X			
Adverse events check	X[J]	X	X	X	X
Concomitant medication collection[I]	X	X	X	X	X
Harvey Bradshaw Index (HBI)/ Simple Clinical Colitis Activity Index (SCCAI)	X	X	X	X	X
IBD-Control questionnaire		X			X
Treatment acceptability questionnaire		X			X
Clinical blood tests	X	X	X	X	X
HLA DQA1*05 (research sample)	X				
Thioguanine nucleotides, TGN (research sample)		X[D]			X[G]
Infliximab (IFX) level (research sample)		X	X	X	X
Anti-drug antibodies (research sample)		X	X	X	X
Stool sample collection for faecal calprotectin	[E]	X[E]	X[H]	X[EH]	X[E]
Whole blood sample for exploratory endpoint and future research (GSTT only)	X				X

*Withdrawn participants will be asked to complete a final early termination visit 8 weeks after their last study visit, i.e. at the time of what would have been their next scheduled study visit. For example if a participant withdraws after W8, their early termination visit should be completed at W16 (it replaces week 16).
A: Blood pressure, pulse, saturation and temperature
B: height at screening only
C: no minimum requirements for the physical exam, but at discretion of the assessing investigator
D: does not need to be repeated if done within 8 weeks of randomisation
E: The stool collection instructions and stool container should be dispensed to the patients at the visit prior to the collection visit
F: if no physical examination is required, the Dr review can be done remotely
G: If still on thiopurine by week 24
H: not required per protocol but investigator may want to measure calprotectin if needed to monitor disease activity
I: vitamins or probiotics do not need to be recorded
J: only SAEs, IMEs and pregnancies need to be recorded (and reported) between screening and baseline.
GSTT: Guy's and St Thomas' NHS Foundation Trust

5 Trial medication

5.1 Investigational Medicinal Product

The Investigational Medicinal Product (IMP) evaluated in this trial is the immunomodulator, which is used alongside the SC CT-P13 (a NIMP) for the treatment of IBD. The immunomodulators prescribed for IBD are Azathioprine and Mercaptopurine.

The IMP will continue to be prescribed to participants as part of their standard of care by their general practitioner (GP), who will issue a prescription for the participant to pick up/ be delivered the medication from their local pharmacy (for participants randomised to continuing the immunomodulator). The GP will be informed of their patient's participation in the trial, including the randomisation allocation to continue or stop taking the immunomodulators, to ensure continued supply of IMP to the participant throughout the trial, for those randomised to continuing taking the immunomodulators. Likewise the GP will be informed if their patient are randomised to stopping the immunomodulators, in order to avoid waste.

There are numerous licensed and commercially available products containing azathioprine/ mercaptopurine as active ingredient used for the treatment of UC and CD. The specific product dispensed will depend on individual healthcare providers and pharmacies, therefore these drugs are usually prescribed as the generic active ingredient. Accordingly, there are no protocol restrictions regarding which brand, manufacturer or suppliers of product are prescribed to participants taking part in this trial, as they are all widely used in clinical practice[10]. Therefore the dosage form, label and packaging will vary between participants and there is no trial-specific labelling required.

5.2 Dosing regime

Immunomodulator drugs are taken by mouth, usually once a day, with or just after food or a meal, at a dosage that depends on age, body weight and severity of disease activity. In order to be included in the trial participants will have taken immunomodulators for at least 3 months, at stable dose for at least 4 weeks at the time of commencement of SC CT-P13.

Participants will start/ stop taking immunomodulators as part of this trial from the baseline visit, i.e. between screening and baseline participants will continue taking their immunomodulators as prior to the trial (as per standard of care). The maximum trial duration, i.e. of ongoing exposure to the IMP per participant, is 25 weeks.

Participants randomised to continuing their immunomodulator will do so at the same stable dose and frequency that they were taking for the last 4 weeks prior to commencement of SC CT-P13 (as per standard of care). If changes in dose or frequency are deemed necessary during the trial, these changes are allowed at the discretion of the treating investigator and will be

recorded in the database. If the investigator and patient make a decision to stop taking the immunomodulator during the trial, the date and reason will be recorded and the participant will be withdrawn with an early termination visit (see section 6.8).

Participants randomised to stopping their immunomodulator, who need to go back on immunomodulators would do so at a dosage determined by the treating investigator and will be withdrawn from the trial with an early termination visit (see section 6.8).

5.3 IMP risks

For reference safety information for the IMPs, investigators should refer to the relevant current summary of product characteristics (SmPC) for each product.

As a generic guidance the following side effects and contraindications are extracted from the current British National Formulary (BNF) at the time of writing this protocol (BNF 83 March - September 2022), however clinicians should use the most recent BNF information for making clinical decisions.

5.3.1 Risks of stopping immunomodulators

There is a possibility that stopping the immunomodulator tablets will risk a relapse of the underlying IBD. To minimise this risk participants will be closely monitored with frequent research visits. At each visit, investigators will look for indicators of worsening disease activity. This include changes in symptoms (HBI/SCCAI scores), physical examination if one is needed and signs of inflammation by means of blood (CRP) and stool (calprotectin) testing. Participants will be asked to get in touch with their local research team immediately if they think that symptoms are starting to get worse.

5.3.2 Known side effects of immunomodulators

Participants will have taken the immunomodulator tablets before the trial, so some side effects, at an individual level, may already be known to them.

AZATHIOPRINE

General side-effects

Common (1 in 100 to 1 in 10) or very common (greater than 1 in 10)

- Bone marrow depression (dose-related); increased risk of infection; leucopenia; pancreatitis; thrombocytopenia

Uncommon (1 in 1000 to 1 in 100)

- Anaemia; hepatic disorders; hypersensitivity

Rare (1 in 10 000 to 1 in 1000) or very rare (less than 1 in 10 000)

- Agranulocytosis; alopecia; bone marrow disorders; diarrhoea; gastrointestinal disorders; neoplasms; photosensitivity reaction; pneumonitis; severe cutaneous adverse reactions

Frequency not known (frequency is not defined by product literature or the side-effect has been reported from post-marketing surveillance data)

- Nodular regenerative hyperplasia; sinusoidal obstruction syndrome

Specific side-effects

Frequency not known

- With oral use: nausea

Side-effects may require drug withdrawal.

- Hypersensitivity reactions (including malaise, dizziness, vomiting, diarrhoea, fever, rigors, myalgia, arthralgia, rash, hypotension and renal dysfunction) call for immediate withdrawal.
- Neutropenia and thrombocytopenia Neutropenia is dose-dependent. Management of neutropenia and thrombocytopenia requires careful monitoring and dose adjustment.
- Nausea is common early in the course of treatment and usually resolves after a few weeks without an alteration in dose. Moderate nausea can be managed by using divided daily doses, taking doses after food, prescribing concurrent antiemetics or temporarily reducing the dose.

MERCAPTOPURINE

General side-effects

Common (1 in 100 to 1 in 10) or very common (greater than 1 in 10)

- Anaemia; appetite decreased; bone marrow depression; diarrhoea; hepatic disorders; hepatotoxicity (more common at high doses); leucopenia; nausea; oral disorders; pancreatitis; thrombocytopenia; vomiting

Uncommon (1 in 1000 to 1 in 100)

- Arthralgia; fever; increased risk of infection; neutropenia; rash

Rare (1 in 10 000 to 1 in 1000) or very rare (less than 1 in 10 000)

- Alopecia; face oedema; intestinal ulcer; neoplasms; oligozoospermia

Frequency not known (frequency is not defined by product literature or the side-effect has been reported from post-marketing surveillance data)

- Photosensitivity reaction

5.3.3 Cautions

AZATHIOPURINE

- Reduce dose in elderly
- reduced thiopurine methyltransferase activity

MERCAPTOPURINE

- Reduced thiopurine methyltransferase activity

5.3.4 Risks to participants who become pregnant during the trial

Pregnant women and women of child bearing potential who are planning to get pregnant during the trial (from screening to W24) will not be included. However, if a woman was to become pregnant during the trial they do not need to be withdrawn and their management will be as per their treating investigator.

The CI or PI at each site will be responsible for reporting any pregnancy to the Sponsor via the SAE report forms. Each pregnancy will be followed up until the outcome of the pregnancy is known.

5.3.5 Risks and side effects of NIMP: SC CT –P13

For reference safety information for the NIMP, investigators should refer to the relevant current summary of product characteristics (SmPC).

The subcutaneous injections of infliximab have almost identical side effects to the intravenous infliximab, including the following very common side effects (may affect more than 1 in 10 people): stomach pain, feeling sick, viral infections such as herpes or flu, upper respiratory infections such as sinusitis, headache.

The difference to intravenous infliximab is that local side effects may occur due to the injection. These include pain, redness or bruising at the site of the injection.

5.4 Drug accountability

Drug accountability and drug reconciliation are not required for this trial as the supply of immunomodulators to the participants is part of their standard of care.

5.5 Participant compliance

Compliance with IMP will be assessed at weeks 8, 16 and 24/ Early Termination as a subjective estimate by the participant. Participants will be asked to grade their compliance as <25%, between 25-50%, between 50-75% or >75% since the last study visit, where 100% represents IMP taken every day since last study visit.

5.6 Concomitant medications

5.6.1 Recording of concomitant medications

Concomitant medications will be collected from screening until the end of the trial. Vitamins or probiotics do not need to be reported.

5.6.2 Interactions

An extensive list of interactions is listed in the BNF, which should be checked by the prescribing clinician for each product. The following are listed in the BNF as "severe" interactions:

AZATHIOPRINE

- Allopurinol, Bacillus Calmette-Guérin vaccine, Baricitinib, Captopril, Enalapril, Febuxostat, Filgotinib, Fosinopril, Herpes-zoster vaccine live, Imidapril, Influenza vaccine live, Lisinopril, Measles, mumps and rubella vaccine live, Perindopril, Quinapril, Ramipril, Rotavirus vaccine, Trandolapril, Trimethoprim, Typhoid vaccine, oral, Varicella-zoster vaccine, Yellow fever vaccine, live.

MERCAPTOPURINE

- Allopurinol, Bacillus Calmette-Guérin vaccine, Febuxostat, Herpes-zoster vaccine live, Influenza vaccine live, Measles, mumps and rubella vaccine live, Rotavirus vaccine, Trimethoprim, Typhoid vaccine oral, Varicella-zoster vaccine, Yellow fever vaccine live

→ NOTE ALLOPURINOL is often prescribed for patients with IBD and immunomodulators dose is often reduced dose with concurrent use of allopurinol.

5.6.3 Contraception during the trial

In view of the fact that continuation of thiopurines (and infliximab) is standard of care in IBD during pregnancy (as recommended by international guidance[11]) WOCBP, or partners of WOCBP, will not be asked to change their usual contraceptive practice to avoid pregnancy during the trial. Acceptable methods of contraception are complete abstinence, hormonal

and barrier methods, intrauterine device or hormone releasing system, bilateral tubal occlusion and vasectomized partner.

5.6.4 Non-Investigational Medicinal Product (NIMP): SC CT –P13

Participants enrolled into the trial will be taking SC CT-P13 as part of their standard of care. SC CT-P13 comes in the form of a solution for subcutaneous injection in a pre-filled syringe (Remsima SC).

SC CT-P13 is to be administered subcutaneously every 2 weeks at the licensed dose. At the time of writing this protocol the licensed dose is 120mg, starting approximately 8 weeks after discontinuing IV infliximab (i.e. at the time of the baseline visit). The first dose will be administered at the baseline visit, where training will be provided to the participant and/or family member/ friend on how to carry out the self-administration themselves.

SC CT-P13 will be prescribed by the hospital gastroenterology team as part of routine care, and the product is provided to participants via their local home care provider. The research team will make sure that arrangements are in place for the participant to receive the medication ahead of the baseline visit.

6 Selection and Withdrawal of Participants

6.1 Setting

The trial will be conducted in National Health Service Adult Gastroenterology outpatient clinics in the United Kingdom, referred to as 'sites' in the protocol.

6.2 Inclusion Criteria

- Aged 18 years or over
- Diagnosis of Crohn's disease, ulcerative colitis or IBD-U for at least 6 months at the time of commencement of SC CT-P13
- A clinical decision has been made to switch from intravenous infliximab to SC CT-P13
- On stable IV infliximab at 5mg/kg Q8W for at least 22 weeks at the time of commencement of SC CT-P13
- On azathioprine or mercaptopurine for at least 3 months, at a stable dose for at least 4 weeks at the time of commencement of SC CT-P13
- Clinical remission defined by HBI ≤4 or SCCAI ≤2 at screening
- Infliximab levels above or equal to the lower therapeutic level (as per local lab) at the time of the final or penultimate IFX infusion
- Written informed consent to participate

- Sufficient English to understand the study and sign informed consent, or available local interpreting service

6.3 Exclusion Criteria

- Not willing or able to switch to subcutaneous (SC) treatment
- Evidence of clinically active severe infections such as, bacterial sepsis, active viral infection and opportunistic infections. Severity as judged by the investigator
- Any clinically significant test results that in the opinion of the investigator should exclude the participant
- In the opinion of the investigator, patient in whom withdrawal of the thiopurine would not be appropriate
- Known allergy/ hypersensitivity/ intolerance to the active substance or excipients, or patients taking any medications which are contraindicated as per the IMPs SmPCs
- Participation in an investigational trial that involves ongoing treatment with an investigational medicinal product at baseline
- Pregnant women and women of child bearing potential who are planning to get pregnant during the trial

6.4 Identification of Participants

Suitable patients for the clinical trial will be identified from gastroenterology clinics at each site by the direct care team. Only the direct care team can identify and approach potential participants without prior consent. Potential participants will be asked to provide verbal consent for a member of the research team to contact them to discuss the study further. The participants' medical history and results will be reviewed by the local research team to assess potential eligibility for participation in the study. A fully-anonymised pre-screening log will be used to record the number of participants potentially eligible but not entered into the trial in order to fulfil CONSORT reporting guidelines.

6.5 Consent

The Principal Investigator (PI) retains overall responsibility for the conduct of research at their site, this includes the taking of informed consent of participants at their site. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. If delegation of consent is acceptable then details should be provided.

Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial and are out-with standard routine care at the participating site (including the collection of identifiable participant data unless the trial has

prior approval from the Confidentiality Advisory Group (CAG) and the Research Ethics Committee (REC)).

A patient information sheet (PIS) will be provided to facilitate the informed consent process. Investigators must ensure that they adequately explain the aim, trial procedures, potential risks and benefits of taking part in the trial. The patient should be given ample time (at least 24 hours) to read the PIS and to discuss their participation with others outside of the clinical research team. The patient must be given the opportunity to ask questions which should be answered to their satisfaction. The right of the patient to refuse to participate without giving a reason must be respected.

If the patient decides to participate in the trial they will be asked to sign and date the latest approved version of the Informed Consent Form (ICF). The form must also be signed and dated by the delegated investigator who conducted the informed consent process. Details of the informed consent discussions should be recorded in the patient's medical notes. A copy of the signed ICF and PIS should be provided to the patient and a copy will be kept in their medical records. The original signed consent forms will be kept in the Investigator Site File. A Consent and Enrolment log will be maintained by the site.

6.6 Subject Confidentiality

To protect the privacy and identity of trial patients, subjects will be assigned a unique patient trial identifier upon enrolment, created electronically in the trial database. Only Investigators and authorised staff at the trial site will be in possession of documents that link patient names to patient trial identifiers (i.e. ICF and Consent and Enrolment Log). It is the responsibility of the PI to ensure that these documents are treated in a confidential manner and stored securely.
In case any medical records containing patient data (e.g. laboratory results, medical reports) have to be sent to the Sponsor or external parties, the trial team will remove the patient's name as well as any other potential identifiers (e.g. hospital number, date of birth) and encode the documents with the appropriate patient trial identifier. Safety reports transmitted to the Sponsor and to the regulatory authorities and Ethics Committees will also be pseudo-anonymised with this unique patient number. All data collected as part of the study will be regarded as strictly confidential.

6.7 Randomisation Procedure / code break

At the baseline visit, once study eligibility has been confirmed by a delegated investigator, participants will be randomised to either continue their thiopurine throughout the study or to stop. Randomisation will be stratified by HLA DQA1*05 status.

Randomisation will only be performed once screening has been completed, blood test results have been reviewed and eligibility re-confirmed at baseline.

A secure computerised web-based programme, provided by MedSciNet, will be used to generate the treatment allocation. Appropriately delegated members of the research team will randomise patients by completing an on-screen form via their personal MedSciNet account. All parties will be aware of the participants' allocation.

Emergency code breaking is not required as the treatment is open label.

6.8 Withdrawal of Participants

Participants have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study in the event of inter-current illness, AEs, SAEs, SUSARs, protocol violations, cure, administrative reasons or any other reasons deemed appropriate. It is understood by all concerned that an excessive rate of withdrawals can render the study un-interpretable; therefore, unnecessary withdrawal of participants should be avoided. Should a participant decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible.

Where a decision is made by the participant and/or investigator to withdraw from trial medication (immunomodulator), from the SC CT-P13 or to revert back to IV infliximab infusions, the participant will be withdrawn from the trial. Withdrawn participants will be asked to complete a final early termination visit 8 weeks after their last study visit, i.e. at the time of what would have been their next scheduled study visit. For example if a participant withdraws after W8, their early termination visit should be completed at W16 (it replaces week 16).

Participants who seem to be lost to follow-up will be documented as withdrawals, however the research teams should make reasonable efforts to reach out to the participants via either telephone/ email/ post at least 3 times on 3 separate days, before withdrawing participants from the trial.

Withdrawn participants will not be replaced**.**

6.9 Expected Duration of Trial

It is expected that each participant will be in the treatment period for a maximum of 25 weeks post randomisation (individual patient follow-up duration).

The estimated recruitment period is 12 months. The total estimated duration from First Patient First Visit (FPFV) until the end of the trial is 20 months. The end of the trial is defined as the date of the final database lock, once all participants have completed all the study related visits, and the data has been entered in the eCRF and cleaned.

6.10 Treatment after the end of the trial

Once the final visit for the trial is completed (Week 24 or Early Termination) the patient and their treating clinician will decide the best course of treatment going forward, i.e. to resume/ continue/ stop thiopurines as part of standard of care.

6.11 Co-enrolment with other trials

Co-enrolment with other trials which involve treatment with an investigational medicinal product is not permitted, however observational studies are allowed.

7 Trial procedures

7.1 Assessments per Trial Visit

Please refer to section 4.4 for trial schedule of events

7.1.1 Screening (-9 weeks to - 2 weeks prior to baseline)

- Informed Consent
- Inclusion/Exclusion criteria assessment by a study physician appropriately delegated in the delegation log, after the participant has signed the informed consent form.
- Pregnancy test for WOCBP (urine test, confirmed with serum test if result is positive)
- Demographics
- Vital signs: Blood pressure, pulse, saturation and temperature
- Height and weight
- Doctor review ± physical examination, as per delegated clinician's discretion
- Medical and smoking history
- Adverse events check. Only SAEs, IMEs and pregnancies need to be recorded (and reported) between screening and baseline.
- Concomitant medication collection
- SCCAI/HBI calculation
- Clinical blood samples
- Research blood samples: HLA DQA1*05 (for randomisation stratification)
- Give participant stool collection instructions and container

At Guy's and St Thomas' NHS Foundation Trust only:

- Whole blood sample for exploratory analysis
- Whole blood samples for future research (if participant has consented to this)

7.1.2 Baseline visit (week 0)

- Repeated Inclusion/Exclusion criteria assessment by a study physician appropriately delegated in the delegation log, prior to commencement of any other interventions
- Pregnancy test for WOCBP (urine test, confirmed with serum test if result is positive)
- Vital signs: Blood pressure, pulse, saturation and temperature
- Doctor review ± physical examination, as per delegated clinician's discretion
- First dose of SC CT-P13 and training to the participant and/or family member/ friend on how to carry out the self-administration themselves
- Randomisation
- Adverse events check. Only SAEs, IMEs and pregnancies need to be recorded (and reported) between screening and baseline.
- Concomitant medication collection
- SCCAI/HBI calculation
- IBD-Control questionnaire and treatment acceptability questionnaire
- Clinical blood samples
- Research blood samples: infliximab level, anti-drug antibodies and thioguanine nucleotides (TGN)
- Stool sample collection for faecal calprotectin (The stool collection instructions and stool container(s) should be dispensed to the patients at the visit prior to the collection visit)

7.1.3 Week 8 (± 1 weeks) and 16 (± 1 weeks) visits

- Vital signs: Blood pressure, pulse, saturation and temperature
- Doctor review ± physical examination, as per delegated clinician's discretion
- IMP compliance check
- Adverse events check
- Concomitant medications collection
- SCCAI/HBI calculation
- Clinical blood samples
- Research blood samples: Infliximab level and anti-drug antibodies
- Stool sample collection for faecal calprotectin is not required at W8 and W16 however investigators may carry them out if they feel they are needed for disease worsening monitoring, in which chase the results will be recorded in the database
- Give participant stool collection instructions and container (week 16 only)

7.1.4 Week 24 (± 1 weeks)/ Early termination visit

Withdrawn participants will be asked to complete a final early termination visit 8 weeks after their last study visit, i.e. at the time of what would have been their next scheduled study visit. For example if a participant withdraws after W8, their early termination visit should be completed at W16 (it replaces week 16).

- Weight
- Vital signs: Blood pressure, pulse, saturation and temperature
- Doctor review ± physical examination, as per delegated clinician's discretion
- IMP compliance check
- Adverse events check
- Concomitant medications collection
- SCCAI/HBI calculation
- IBD-Control questionnaire and treatment acceptability questionnaire
- Clinical blood samples
- Research samples: infliximab level, anti-drug antibodies, TGN profile (if still taking a thiopurine at week 24)
- Stool sample collection for faecal calprotectin (The stool collection instructions and stool container(s) should be dispensed to the patients at the visit prior to the collection visit)

At Guy's and St Thomas' NHS Foundation trust only:

- Whole blood sample for exploratory analysis
- Whole blood samples for future research (if participant has consented to this)

7.2 Laboratory Tests

7.2.1 Clinical Blood Tests

Approximately 15 mL of blood per visit will be collected from participants for the processing of clinical samples. All clinical blood tests will be taken as per standard of care in the appropriate vacutainers and analysed by the hospitals local laboratories, with results available on the patient records. The results will be recorded in the trial database by the research team.

Clinical blood tests include:

- Haematology: full blood count (FBC), including white cell count (WCC), neutrophils, lymphocytes, monocytes, eosinophils, basophils, red blood cell count, haemoglobin (Hb) and platelet count
- Liver profile: albumin, alkaline phosphatase, total bilirubin, alanine aminotransferease (ALT)/ aspartate aminotransferase (AST) as per local procedures
- Renal profile: sodium, potassium and creatinine
- CRP
- Infliximab levels used for eligibility assessment are historical clinical tests

7.2.2 Research Blood Tests

Approximately 10-15 mL of blood per visit (up to 30ml at Guy's and St Thomas' NHS Foundation Trust at baseline and W24/ET due to optional samples) will be collected from participants for the processing of research samples. Research samples will be analysed at the central lab, Viapath laboratories, located at St Thomas' Hospital, London. These samples will be psudoanonymised (labelled with participant ID, sample type and date of collection). Further details on processing and storage requirements for research sampled are described in the trial specific laboratory manual.

- HLA DQA1*05, at screening only, will be collected in a 10ml EDTA tube (purple top) and sent to the central lab straight after the visit, in the post, using packaging and labels provided by the sponsor. No processing required at site
- Infliximab levels and antibodies, at Baseline, Weeks 8, 16 and 24 will be collected in 10ml SST tubes (yellow tops), processed at site to extract serum, and stored frozen at -20C. The serum aliquots will be sent to the central lab in dry ice in batches, using medical courier arranged by the sponsor. Details on processing found in the trial specific laboratory manual
- TGN samples, at baseline and Week 24, will be collected in a >4ml EDTA tube (purple top) and sent to the central lab straight after the visit (must be within 3 days of the visit), in the post, using packaging and labels provided by the sponsor. No processing required at site. TGN profile at baseline does not need to be repeated if done as a clinical sample within 8 weeks prior to baseline. TGN at week 24 does not need to be collected if participant is no longer taking immunomodulators

The following samples will be collected at the lead site only (Guy's and St Thomas' NHS Foundation Trust), transported by foot to the Peter Gorer Department of Immunobiology, at Guy's Hospital, to be frozen and stored in liquid nitrogen until analysis:

- A whole blood sample, at screening and Week 24/ Early termination, collected in a 10ml lithium heparin coated tube (green top), to be used for the exploratory endpoint of the trial
- An additional optional whole blood sample, at screening and Week 24/ Early termination, also collected in a 10ml lithium heparin coated tube (green top), to be stored for future ethically approved studies (if the participant has explicitly consented for this). This sample will be stored at the Peter Gorer Department of Immunobiology, at Guy's Hospital, until the end of this trial, when it will be transferred to King's College London Infectious Diseases Biobank (KCL IDB). Any samples not transferred into the biobank or a new study by the end of this trial will be destroyed.

7.2.3 Stool samples

Stool samples collection instructions and containers will be dispensed to the patients at the visit prior to the collection visit. The samples will analysed in the local laboratory, as per local procedures.

Stools samples for calprotectin measurement are only required per protocol at baseline and W24/ET. However if the investigator feels necessary to assess levels of calprotectin for the purpose of disease monitoring they may do so and report the results in the database.

8 Safety Assessments

All subjects will undergo routine clinical trial visits throughout the trial.

8.1 Specification, Timing and Recording of Safety Parameters

IBD patients require monitoring due to the potential complications associated with their condition in terms of loss of response to therapy and the adverse effects of systematic immunosuppression.

The clinical trial visits and assessments have been designed to allow for close and regular safety evaluations of all trial participant. The following measures will be taken to ensure that the maximum safety for the subjects participating in the trial is assured:

- Stringent eligibility criteria to exclude subjects with underlying health issues that could potentially put them at increased risk of developing serious adverse events or reactions
- Regular and thorough patient monitoring during trial visits:
    - Vital signs, clinical blood tests and physical examination will be performed at each trial visit and assessed by the delegated clinician for any clinically significant changes. Significant changes are not pre-defined but judged by the assessing clinician.
    - Assessment of disease activity will be monitored with either SCCAI/HBI and/or objective markers of inflammation with CRP at each trial visit.
    - AEs will be recorded from screening to the final visit (Week 24 visit or Early Termination if withdrawn). Only SAEs, IMEs and pregnancies need to be recorded (and reported) between screening and baseline. All AEs recorded (and SAEs reported) from baseline.

Safety data collected will be recorded contemporaneously in the eCRF, enabling safety information to be interpreted as they emerge.

8.2 Determination of the clinical deterioration in symptoms.

Clinical deterioration will be determined by assessing the HBI/ SCCAI scores and by objectively assessing signs of inflammation, by means of CRP and in some cases (at investigator discretion) by faecal calprotectin monitoring. A definition of clinical deterioration is not provided in this protocol, but judged in the opinion of the delegated clinician assessing the participant as per usual standard of care.

8.3 Procedures for Recording and Reporting Adverse Events

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR): Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the SmPC.

Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- Results in death;
- Is life-threatening;
- Required hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect.

Important Medical Events (IME) & Pregnancy
Defined as events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above and should also be considered serious.
Although not a serious adverse event, any unplanned pregnancy will also be reported via the SAE reporting system.

8.4 Safety Reporting Period

AEs will be recorded from screening to the final study visit (Week 24 visit or Early Termination) however only SAEs, IMEs and pregnancies need to be recorded (and reported) between screening and baseline. All AEs, serious or not, will be recorded (and SAEs reported) from baseline.

The reasoning for recording only SAEs between screening and randomisation is because although participants consent to participate in the trial at the screening visit, there is no change to their standard of care until the baseline visit, when they are randomised to either continue or withdraw the immunomodulators as the intervention under assessment in this trial. Therefore there is no need to record non-serious AEs prior to this point.

Once participants have completed the trial (at week 24 or earlier), they will likely continue the SC CT-P13, with or without thiopurines, as standard of care. This decision to is to be made by the clinical care team and patients themselves, therefore no safety follow up is required as part of the trial (See section 6.10).

8.5 Severity

Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

- Mild: does not interfere with routine activities
- Moderate: interferes with routine activities
- Severe: very difficult or impossible to perform routine activities

8.6 Expectedness

If there is at least a possible involvement of the trial medications, the investigator and sponsor must assess the expectedness of the event. An unexpected adverse reaction is one that is not reported in the current SmPC, or one that is more frequently reported or more severe than previously reported.

The investigator/ Sponsor will refer to the corresponding SmPC for a list of expected toxicities associated with the drugs being used in this trial. If a SAR is assessed as being unexpected, it becomes a SUSAR and it must be reported to the regulatory authorities as per section 8.8.

8.7 Reporting Responsibilities

Guy's and St Thomas' NHS Foundation Trust have delegated the delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 to the King's Health Partners Clinical Trials Office (KHP-CTO).

All SAEs, SARs and SUSARs will be reported immediately (and certainly no later than 24hrs after becoming aware of it) by the Investigator to the KHP-CTO and CI for review in accordance with the current pharmacovigilance policy. All SAEs, SARs and SUSARs (including any follow-up information), will be reported using the KHP-CTO SAE report form.

The KHP-CTO will report SUSARs to the regulatory authority, the MHRA.

The Chief Investigator will report to the relevant ethics committee. Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.

The Chief Investigator and KHP-CTO (on behalf of the Sponsor), will submit a Development Safety Update Report (DSUR) relating to this trial IMP, to the MHRA and REC annually.

The Chief Investigator will submit Annual Progress Reports to the main REC annually.

8.8 Premature termination of the trial

The trial may be terminated prematurely by the Sponsor, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the Trial Steering Committee, regulatory authority or ethics committee concerned. The Sponsor and Chief Investigator reserve the right to stop the trial at any time, for any justifiable reason. In the event of premature termination, the Sponsor will notify the regulatory authorities within 15 days by providing a detailed written explanation. The CI will inform the REC. The affected trial participants will also be informed promptly and appropriate follow-up visits will be arranged. No further participant data will be collected.

The clinical trial may be prematurely terminated at any of the individual recruiting sites for the following reasons:

- Serious and/or persistent non-compliance with trial protocol
- Non-compliance with ethical standards, regulatory requirements or GCP compliance
- Findings uncovered during monitoring visits, audits or inspections that compromise patient safety or suitability of the site to act as a trial centre
- Failure to meet recruitment targets

9 Statistics

9.1 Sample size

Using an alpha of 5%, and assuming that 93.9% remain free from the development of free antibodies at week 24[3] and using a non-inferiority limit of 15%, a sample size of 88 (44 per arm) would be required to exclude a difference between the two groups with 90% power. Assuming 15% drop out rate, this gives a total sample size of 102 participants. Withdrawals will not be replaced.

9.2 Randomisation

Randomisation is at the participant level and will be done in a 1:1 ratio. The HLA DQA1*05 status of each participant will be used to stratify the randomisation process, to ensure that the groups are balanced.

HLA DQA1 will be measured by means of a blood sample at screening. The sample will be sent to the central lab straight after the visit and the results will be returned to the research teams within 2 weeks, ahead of the baseline (randomisation) visit.

At the baseline visit participants will be randomised to either continue their thiopurine throughout the study or to stop them. The HLA DQA1 status will be entered into the randomisation system by the research teams. The randomisation system will be online, username/password protected, hosted by MedSciNet. The research teams will be given access to the system by the trial manager.

Baseline covariates will be compared between the two randomisation arms to observe balance and the success of randomisation without formal statistical testing.

9.3 Efficacy parameters and analysis of Primary Endpoints

The trial's primary efficacy outcome is measured by the presence of free serum infliximab antibodies at week 24 (see section 4.2.1).

Once all data from week 24 are cleaned, the database will be locked and the primary analysis will be performed. The primary analysis will follow the intent-to-treat (ITT) principle. The primary analysis will estimate the difference in the proportion of participants with free positive anti-infliximab antibodies between participants randomised to continuing and stopping immunomodulators at the week 24 time point. The comparison between the two groups will be carried out using z-test for non-inferiority. The difference estimate and associated confidence interval will be reported. Where non-inferiority is found, a one-sided Fisher's exact test or chi-square test will be used as appropriate.

There will be a 14-day window (± 1 week) for the primary time point of interest (week 24). Primary endpoint data outside of this window will be excluded from the main primary analysis. However, a sensitivity analysis including these data will carried out to investigate whether or not results will be different.

Participants who withdraw from the trial between randomisation and Week 24 will not have their primary endpoint measured. Since withdrawals are expected to be minimal, no per protocol primary analysis is planned.

9.4 Efficacy parameters and analysis of Secondary Endpoints

The measurements of secondary endpoints are detailed in section 4.2.2. The data from these measurements will be summarised according to the type of the data as detailed below.

All continuous variables will be summarised by the mean and standard deviation (SD) as well as the median and interquartile range (IQR):

- Infliximab drug levels at each week 8, 16 and 24 by randomisation allocation and by DQA1*05 status (positive and negative)
- Infliximab drug levels at week 8, 16, and 24 regardless of randomisation allocation in
    - participants with baseline TGN concentrations ≥125 pmol/8x108 vs <125 pmol/8x108 RBC
    - and participants with baseline TGN ≥ 235 pmol/8x108 RBC vs <235 pmol/8x108 RBC
- Total anti-Infliximab antibodies at weeks 8, 16, and 24 regardless of randomisation allocation and by HLA DQA1*05 status (positive and negative)
- Total anti-infliximab antibodies by week 24 by randomisation allocation

Categorical data will be summarised by frequency (N) and proportion (%):

- N(%) with free anti-infliximab antibodies at weeks 8 and 16, by randomisation allocation
- N(%) with free anti-infliximab antibodies by week 24, by randomisation allocation
- N(%) with free anti-infliximab antibodies at weeks 8, 16, and 24 in participants with positive and negative HLA DQA1*05 regardless of randomisation allocation
- N(%) with clinically active disease (CAD) by week 24/ Early termination, by randomisation allocation
- N(%) with biochemically active disease (BAD) by week 24/Early termination, by randomisation allocation
- N(%) with both BAD and CAD by week 24/ Early termination, by randomisation allocation
- N(%) who revert back to IV infliximab by week 24, by randomisation allocation

- N(%) who accept switching from IV to SC infliximab treatment measured by treatment acceptability questionnaire at week 24/ Early termination, by randomisation allocation

Tolerability of treatment will be summarised by N(%) of AE and SAEs in patients continuing and discontinuing immunomodulators after switching from IV infliximab to SC CT-P13 at each time point (weeks 8, 16 and 24).

Health-related QoL: The data will be presented as N(%) for each item in all patients completing the IBD-Control questionnaire at baseline and at week 24/ Early termination. The median (IQR) of the IBD-Control-8 and the IBD-Control-VAS scores will be presented.

9.5 Detailed statistical analysis plan

A detailed Statistical Analysis Plan (SAP) will be written by the trial statistician as a separate document to further describe the primary and secondary planned analysis. The SAP will be finalised before recruitment to the trial commences. Should the methods in the SAP differ from the description in this protocol, the methods in the SAP shall prevail.

9.6 Procedures for dealing with missing data, unused data and false data

This section applies only to missing Week 24 primary endpoint data.

To identify key predictors of withdrawal, a logistic regression model will be used to estimate the probability of study completion/ non-completion adjusted on baseline variables such as age, gender, BMI. Two possible scenarios may occur, which will be handled as follows:

1. If no baseline variables effect is noted, the complete case (CC) analysis will be used assuming missing data are Missing Completely at Random (MCAR). This will incur a smaller sample. Figure (i) in Appendix illustrates the impact of a decrease in sample size on power.

2. If differences were found, and the MCAR becomes an unplausible assumption, multiple imputation will be used in a sensitivity analysis considering data Missing At Random (MAR) assumption is plausible (i.e., observed variables such as age predicts missingness of anti-drug antibodies positivity at week 24 estimates). Anti-drug antibodies positivity at an early point (week 8 or week 16 for example) will be used alongside the baseline variables in a multiple imputation process to replace missing data for week 24 endpoint.

10 Trial Management and oversight

10.1 Trial Steering Committee (TSC)

The TSC will be an executive committee, with an independent chair, responsible for the overall supervision on behalf of the Sponsor and Funder and will ensure that the trial is conducted in

accordance with the rigorous standards set out in the UK Policy Framework for Health and Social Care and Guidelines for Good Clinical Practice. The TSC will consist of the Chief Investigator and independent members consisting of a group of experienced doctors, trialists and a patient representative. The roles and responsibilities of the TSC, as well as the frequency of the meetings, is described in the MINIMISE TSC Charter, which will be agreed by all members.

10.2 Independent Data Monitoring Committee (IDMC)

Due to the low risk nature of this trial, which has no planned interim analyses or review of activity data, a separate IDMC has not been established. Cumulative safety data will be reviewed by the TSC.

11 Ethics and Regulatory Approval

11.1 Ethical Conduct of Study

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.
Before commencing the trial, this protocol and related documents will be submitted for review to a chosen NHS Research Ethics Committee (REC), the Health Research Authority (HRA) and to the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation.

During the trial any subsequent amendments to the protocol will also be submitted for REC and MHRA approval, as appropriate. The Chief Investigator will submit Annual Progress Reports to the main REC annually. The Chief Investigator and KHP-CTO (on behalf of the Sponsor) will submit a Development Safety Update Report (DSUR) to the MHRA and REC annually.

The Chief Investigator will submit a final report at conclusion of the trial to the KHP-CTO (on behalf of the Sponsor) and the REC within the timelines defined in the Regulations. The KHP-CTO or delegate will upload the final report to a publicly registered database on behalf of the Sponsor.

12 Quality Assurance

The TSC will be appointed to oversee the conduct of the study.

12.1 Trial monitoring

Monitoring of this trial to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained by the KHP-CTO Quality Team.

A study specific monitoring plan will be developed by the KHP-CTO on the basis of the risk assessment. The KHP-CTO will carry out on-site monitoring to undertake source data verification checks and confirm that records are being appropriately maintained by the PI and pharmacy teams. If on-site visits are not possible, arrangements will be in place for remote monitoring. The site PI will be responsible for ensuring the findings are addressed appropriately. The Clinical Trial Manager will ensure that relevant findings are discussed with the CI and the monitoring reports are filed in the TMF.

13 Data Handling

The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to:

- Participant data will be pseudo-anonymised and all pseudo-anonymised data will be stored on a password protected computer
- Data entered onto the eCRF will be pseudo-anonymised and stored on a secure server
- All hard copies of source data worksheets and ISFs will be kept in a locked office within the trial site
- All trial data will be stored in line with the *Medicines for Humans Use (Clinical Trials) Amended regulations 2006* and the *Data Protection Act (and all amendments to follow).*
- All trial data will be archived in line with the Medicines for Humans Use (Clinical Trials) Amended regulations 2006 and as defined in the King's Health Partners Clinical Trials Office Archiving SOP (and all amendments to follow).

14 Data Management

A data management plan will be created for this trial as a separate document.

The data collected for this trial is a combination of standard clinical and laboratory tests results commonly used in the management of patients with IBD.

A validated questionnaire (IBD-control)[6] will be used for the assessment of health related quality of life of trial participants. A non-validated questionnaire will be used for the assessment of treatment acceptability.

Clinical measurements of disease activity include the Harvey Bradshaw Index (HBI)[7] and the Simple Clinical Colitis Activity Index (SCCAI)[8], two validated disease activity indexes widely used in gastroenterology research.

14.1 Data Collection and data entry

The delegated site staff responsible for data entry will be trained in the use of the eCRF system. Data entered in the eCRF system must be consistent with source data. All applicable fields in an eCRF page should be completed and if data are not available, this should be clearly indicated on the form.

The PI may delegate data entry into the database, but is ultimately responsible for submitting a complete set of eCRFs for each enrolled patient.

Any supportive paper documentation (including details of any SAE) transmitted from the investigators to the Sponsor should be clearly marked with the trial name, patient trial identifier and patient age. Any personal information, including the name of the patient, should be removed or rendered illegible to preserve individual confidentiality.

14.2 Specification of Source data

Source data are defined as all the information in original records (and certified copies of original records) of clinical findings, observations or other activities that are necessary for the complete reconstitution and evaluation of the trial.

Source data must be available at the trial centre, to authenticate the existence of the study participants and substantiate the integrity of the data in the trial database. An eCRF is a data entry screen and does not constitute source data. The data entered into an eCRF should be verifiable with original source records.

Source documentation for the study includes, but is not limited to:

- Informed consent forms
- Medical records/ clinical reports/ laboratory reports/ hospital correspondence/ patient questionnaires

Inconsistencies between the source data and eCRF entries will be raised using data queries, which will prompt the trial site to clarify, correct or confirm discrepancies. At the end of the study, once all the data reported on the database has been monitored and cleaned, the eCRF will be locked. The Chief Investigator is responsible for producing a clean data set for the final statistical analysis.

14.3 Direct Access to Source Data and Documents

The Principal Investigators must allow the Sponsor, designated trial monitors, and when

necessary, members of the Ethics Committee or representatives of the regulatory authorities to review, monitor, audit and/or inspect the trial by providing direct access to source data and other documents (e.g. patients' case sheets, blood test reports, X-ray reports, histology reports etc.). During such activities, the confidentiality of personal data will be respected at all times. By signing the ICF, the recipient will specifically consent to direct access to their medical records and source documentation for the purpose of source data verification (SDV) and regulatory inspection.

14.4 eCRF Database

An electronic Case Report Form (eCRF) will be designed using the industry-standard secure database called MedSciNet[Ltd], which is fully validated and regulatory compliant. This is a web-based platform for electronic data capture. The eCRF will be designed in collaboration with the trial statisticians and trial team.

The eCRF platform will automatically create a protected audit trail for all data entries and changes. Amendments to eCRF data will be recorded in the audit trail with a time and date stamp, along with a user-specified reason for the implemented change.

14.5 eCRF Database Access

All access to the MedSciNet[Ltd] data system is controlled using a Username/Password login. Passwords are encrypted using a PBKDF2 algorithm with a different salt for each user and calculating hash 1000 times before storing in the database. Accounts are created and controlled by Administrative users of the system as identified by the Chief Investigator. The data is stored in the CSAM MedSciNet eCRF servers and meet all MHRA requirements for CTIMP data storage. Only the server administrator has access to this server and the core database, via remote connection. The back-up process consists of:

- Full backups once per week
- Differential backups once every day
- Transaction log backups every hour and
- File system backups once per day.

15 Publication Policy

All data and results generated from this trial are confidential. Agreement from the Sponsor will be required prior to the disclosure of any trial related data.

It is intended that the results of the trial will be submitted for publication in a peer-reviewed scientific journal. Results may also be reported and disseminated at local academic, clinical and patient meetings and at national and international conferences.

16 Insurance / Indemnity

Guy's and St Thomas' NHS Foundation Trust, as the Sponsor, will provide cover under its no fault compensation insurance. It will cover for payment of damages or compensation in respect to any claim made by a research subject for bodily injury arising out of participation in the clinical trial.

17 Financial Aspects

17.1 Funding

The clinical trial is funded by a grant from Celltrion Healthcare specific for this investigator initiated study.

17.2 Patient Travel Expenses

Participants will be reimbursed for reasonable travel expenses incurred to attend trial visits.

18 Archiving

At the end of this trial, all trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the 2018 Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Sponsor's Archiving Standard Operating Procedure (SOP).

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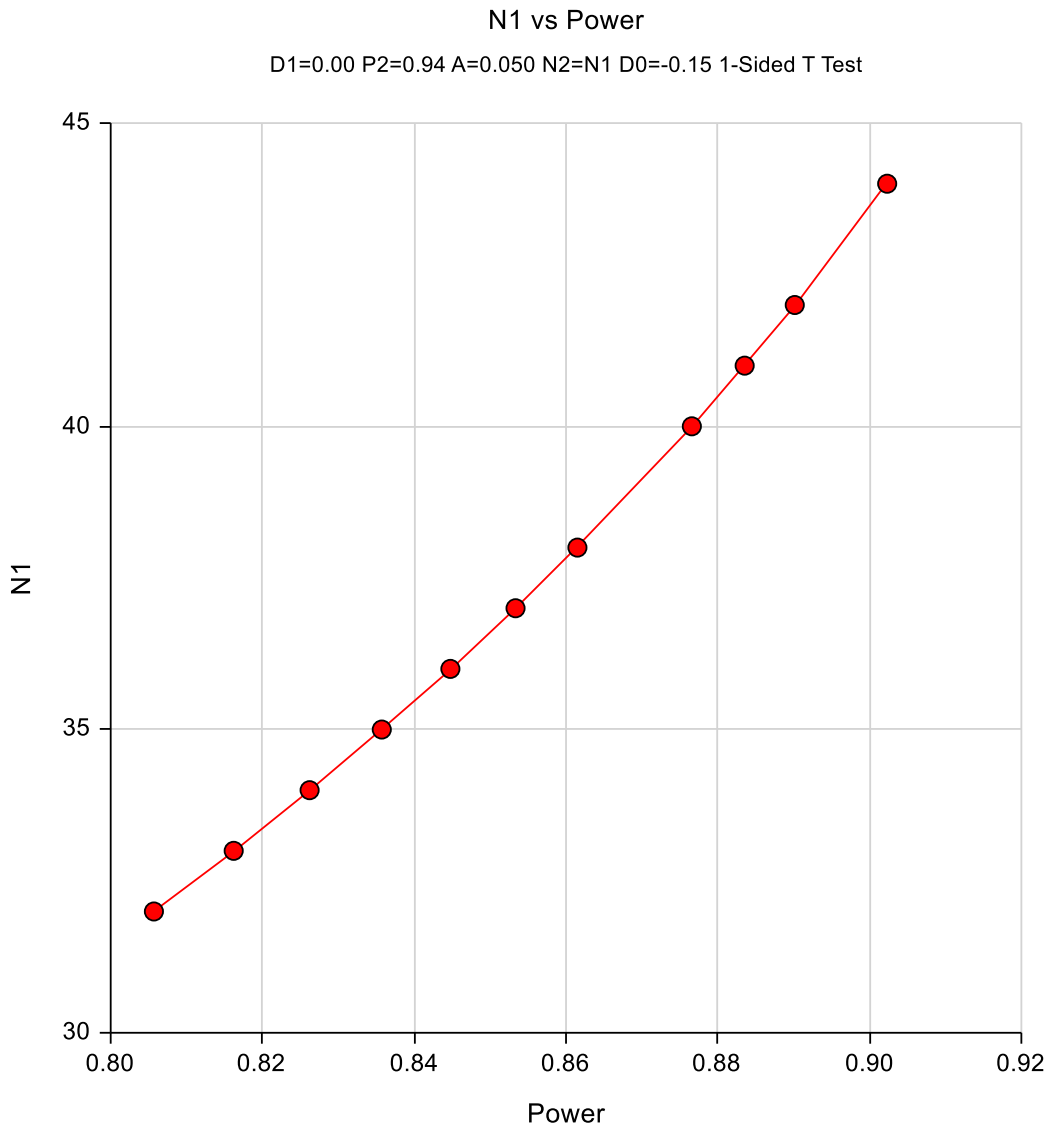
20 Appendix

Figure (i)
Non-Inferiority Tests for the Difference Between Two Proportions



Definitions

N1, N2, are the evaluable sample sizes at which power is computed. The plot was based on the final evaluable sample size with no drop out (D1=0.00). The sample size was however adjusted to allow for D1=15%. Making the total target sample size N=102

P2=93.9% rounded to 94% (0.94)

P2: the proportion for the standard, reference, or control group.

A: Alpha (type I Error rate)